PAPD5 INHIBITORS AND METHODS OF USE THEREOF

CLAIM OF PRIORITY

[0001] This application claims priority U.S. Provisional Patent Application Ser. No. 62/727,443, filed on Sep. 5, 2018, and U.S. Provisional Patent Application Ser. No. 62/819,147, filed on Mar. 15, 2019, the entire contents of which are hereby incorporated by reference.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with government support under Grant No. DK107716, awarded by the National Institutes of Health. The government has certain rights in the invention.

TECHNICAL FIELD

[0003] The present disclosure relates to compounds that inhibit PAP Associated Domain Containing 5 (PAPD5), and to methods of using these compounds to treat conditions such as telomere diseases, and aging-related and other degenerative disorders.

BACKGROUND

[0004] A telomere is a region of repetitive nucleotide sequences at each end of a chromosome, which protects the end of the chromosome from deterioration or from fusion with neighboring chromosomes. The length of a telomere is a key determinant of cellular self-renewal capacity. The telomerase ribonucleoprotein maintains telomere length in tissue stem cells, and its function is critical for human health and longevity.

[0005] Short telomeres, due to genetic or acquired insults, cause a loss of cellular self-renewal and result in life-threatening diseases, for which there are few if any effective medical therapies. In these diseases involving short telomeres, e.g., aplastic anemia, pulmonary fibrosis, hepatic cirrhosis, bone marrow failure, etc., there is an unmet clinical need for new therapies.

SUMMARY

[0006] Poly(A) ribonuclease (PARN) mutations can result in the accumulation of 3' oligo-adenylated forms of nascent Telomerase RNA Component (TERC) RNA transcripts, which are targeted for destruction, thus causing telomerase deficiency and telomere diseases. Disruption of the non-canonical poly(A) polymerase PAP Associated Domain Containing 5 (PAPD5; also known as Topoisomerase-related function protein 4-2 (TRF4-2)) may restore TERC levels, telomerase activity, and telomere elongation in PARN-mutant patient cells.

[0007] In one general aspect, the disclosure relates to a method of treating a disease or condition selected from:

[0008] disorder associated with telomere or telomerase dysfunction; and/or

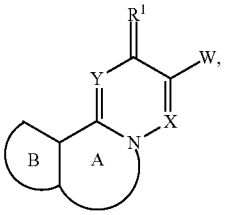
[0009] a disorder associated with aging; and/or

[0010] a pre-leukemic or pre-cancerous condition; and/or

[0011] neurodevelopmental disorder,

the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I):

(I)



or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising same.

[0012] In another general aspect, the disclosure relates to a method of treating a disease or condition selected from:

[0013] disorder associated with telomere or telomerase dysfunction; and/or

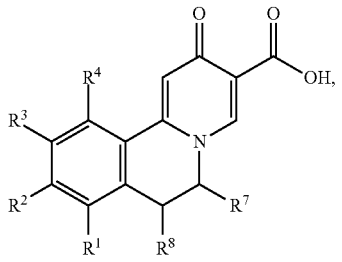
[0014] a disorder associated with aging; and/or

[0015] a pre-leukemic or pre-cancerous condition; and/or

[0016] neurodevelopmental disorder,

the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (II):

(II)



or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising same.

[0017] In yet another general aspect, the disclosure provides a method of modulating ex vivo expansion of stem cells, the method comprising contacting the cells with an effective amount of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof.

[0018] In yet another general aspect, the disclosure provides a method of modulating non-coding RNAs in a cell, the method comprising contacting the cell with an effective amount of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof.

[0019] In yet another general aspect, the disclosure provides a method of expanding a cell, the method comprising culturing the cell in the presence of an effective amount of a compound f Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof.

[0020] In some embodiments, the present application provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the present application provides a compound of Formula (II), or a pharmaceutically acceptable salt thereof.